REMARKS

The Amendments

In order to advance prosecution, Applicants have amended claim 1 and dependent claims 3, 10, 11-17, 18-21, 30 and 31 and have canceled claims 2, 4-9, and 22-29. Specifically, claim 1 has been amended to recite a double-stranded nucleic acid molecule comprising a sense strand and an antisense strand about 18 to about 27 nucleotides in length, wherein the antisense strand comprises sequence complementary to human ICAM nucleotide sequence comprising SEQ ID NO:439, and wherein the double-stranded nucleic acid molecule further comprises at least two different chemically modified nucleotides. Support can be found in the specification at, for example, pages 8, 9, 11, 16, 17, 55, 74, 79, and Tables I and II. Claims 3, 10, 11-17, 18-21, 30 and 31 have been amended to recite a double-stranded nucleic acid molecule. Support for the amendment can be found throughout the specification.

Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

Oath/Declaration

Applicants have enclosed a new declaration. Applicants respectfully request entry of the declaration in place of the originally-filed declaration.

The Sequence Listing

Applicants have enclosed a new sequence listing and request its entry in place of the previously entered sequence listing. The sequence listing adds SEQ ID NO:439. The sequence represents GenBank entry NM_000201 (see Tables I and II). The version of NM_000201 appearing in the sequence listing as SEQ ID NO:439 appeared in GenBank on October 31, 2000. The sequence listing adds no new matter and applicants respectfully request its entry.

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Objection to Claim 1

Claim 1 has been objected to for lacking the word "a" prior to the phrase "nucleotide sequence." The claim has been amended to insert the work "a" as requested. Applicants respectfully request withdrawal of the objection.

Rejection of Claims 1-31 Under 35 U.S.C. § 112, first paragraph

Claims 1-31 stand rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 2, 4-9, and 22-29 have been canceled. Therefore, the rejection is moot as applied to these claims. Applicants respectfully traverse the rejection as it applies to claims 1, 3, 10, 11-17, 18-21, 30 and 31.

The Office Action asserts that although the specification as filed discloses siNA sequences targeted to ICAM, the specification does not provide information regarding what structure directs cleavage of any ICAM RNA via RNAi. The Office Action concludes that the skilled artisan would not be able to envisage the entire genus of siNA molecules that would direct cleavage of any ICAM RNA. Applicants respectfully disagree with this argument, however, in the interest of expediting prosecution, claim 1 has been amended to remove the functional language "directs cleavage of a huntingtin (ICAM) RNA via RNA interference." Claim 1 as amended is directed to a double-stranded nucleic acid molecule comprising a sense strand and an antisense strand about 18 to about 27 nucleotides in length, wherein the antisense strand comprises sequence complementary to human ICAM nucleotide sequence comprising SEQ ID NO:439, and wherein the double-stranded nucleic acid molecule further comprises at least two different chemically modified nucleotides. The claim as amended is fully supported by the written description of the application as discussed in detail below. Accordingly, applicant respectfully requests withdrawal of the 35 U.S.C. §112, first paragraph, rejection.

Priority

The Office Action alleges that the instant application is not entitled to priority to International Patent Application PCT/US03/05028 and U.S. Provisional Applications 60/358,580, 60/363,124, 60/386,782, 60/406,784, 60/408,378, 60/409,293, and 60/440,129. The Applicant respectfully disagrees.

The present application claims priority to, *inter alia*, 60/363,124 (the '124 application), filed March 11, 2002. The claims presented above all find support in, *inter alia*, the '124 application. The Office specifically alleges that although the prior applications disclose siNA

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molecules, they fail to discuss a siNA molecule that targets ICAM RNA. However, the '124 application teaches siNA molecules targeted to ICAM RNA in Table III of the application (entry in Table III for GenBank Accession No. NM_000201). Furthermore, support for chemically synthesized double-stranded nucleic acid molecule can be found at, *inter alia*, p. 3, lines 15-17; p. 32, lines 11-12; p. 35, lines 29-30, and p. 60, line 20; complementarity between the first and second strands at, *inter alia,* p. 12, lines 4-7, p. 19, lines 11-14, p. 20, lines 16-20, p. 21, lines 3-6, and p. 25, lines 17-29; one strand having between 18-27 nucleotides complementary to human ICAM nucleic acid sequence at, *inter alia,* p. 18, lines 1-5, p. 12, line 6, p. 383, entry in Table III for GenBank Accession No. NM_000201; and at least two different modified nucleotides at, *inter alia,* p. 5, line 13 to page 15, line 9, and p. 36, line 1 to page 37 line 31.

Support for the dependent claims can also be found in, *inter alia*, the '124 application:

Claim	Support
3	One or more ribonucleotides: p. 15, lines 3-9
10	Sense strand connected to antisense strand via linker molecule: p. 19, lines 20-21, 25, 28, p. 20 line 15, p. 38 lines 17-29
11	Polynucleotide linker: p 12, lines 13-26, p. 38, lines 18-29
12	Non-nucleotide linker: p 12, lines 13-26
13	One or more pyrimidine nucleotides present in sense strand are 2'-O-methyl pyrimidine nucleotides: p. 10, lines 13, 27, p. 11, lines 8, 22
14	One or more purine nucleotides present in the sense strand are 2'-deoxy purine nucleotides: p. 6, lines 14-15
15	One or more pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides: p. 10, lines 13-14, 27, p. 11, lines 8-9, 22
16	Sense strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand: p. 10, lines 6-7, 20-21, p. 40, lines 1-18
17	Terminal cap moiety is inverted deoxy abasic moiety: p. 5, line 16, p. 14, lines 10-13, p. 40, lines 4-18.
18	One or more pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides: p. 10, lines 13-14, 27, p. 11, lines 8-9, 22
19	One or more purine nucleotides in antisense strand are 2'-O-methyl purine nucleotides: p. 6, lines 14-15
20	One or more purine nucleotides present in the antisense strand are 2'-deoxy

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Claim	Support
	purine nucleotides: p. 6, lines 14-15
21	Terminal phosphorothioate internucleotide linkage at 3' end of antisense strand: p. 9, lines 24-25
30	Terminal phosphate group: p. 8, line 26 to p. 9, line 13
31	Composition comprising the double-stranded nucleic acid molecule in a pharmaceutically acceptable carrier or diluent: p. 18, lines 15-19

Therefore, the instant application is entitled to a priority date of at least March 11, 2002.

Rejections Under 35 U.S.C. § 102(a)

Claims 1-11, 14, 20, 21, 23-29, and 31 stand rejected as allegedly anticipated by Reich *et al.*, (US 2004/0220129). Applicant respectfully traverses the rejection. Reich *et al.* was filed on January 13, 2004 and claims priority to U.S. Provisional Patent Application No. 60/440,579, filed January 13, 2003, both of which were filed after the effective priority date of the instant application. Accordingly, Reich *et al.* cannot anticipate the present invention. Applicant respectfully requests withdrawal of the 35 U.S.C. §102 rejection.

Claims 1, 3-9, 14, 20, 23-28, and 31 stand rejected as allegedly anticipated by Kretschermer-Kazemi Far *et al.*, (2003, Nucleic Acids Research, Vol 31: 4417-4424). Applicant respectfully traverses the rejection. Kretschermer-Kazemi Far *et al.* was published in 2003, after the effective priority date of the instant application. Accordingly, Kretschermer-Kazemi Far *et al.* cannot anticipate the present invention. Applicant respectfully requests withdrawal of the 35 U.S.C. §102 rejection.

Rejections of Claims Under 35 U.S.C. § 103(a)

The claims stand rejected as allegedly obvious over Elbashir *et al.*, (EMBO J, 2001), in view of Nyce *et al.* (WO 96/40162), Tuschl *et al.*, (WO 02/44321), Matulic-Adamic *et al.*, (U.S. 5,998,203) and Morrissey *et al.* (US 2003/0206887). The Office Action asserts that claims 36-69 stand rejected; however, claims 1, 3, 13-14, 19-20, and 30-31 are pending. Applicants respectfully request clarification. Applicants will address this rejection as if claims 1-31 were rejected. Claims 2, 4-9, and 22-29 have been canceled. Therefore, the rejection is moot as applied to these claims. Applicants respectfully traverse the rejection as it applies to claims 1, 3, 13-14, 19-20, 30 and 31.

Initially, for the reasons stated above, the instant application has an earlier priority date than Morrissey *et al.* U.S. Publ. No. 2003/0206887. Therefore, Morrissey is not prior art to the instant application. .

The amended claims recite chemically synthesized double-stranded nucleic acid molecules comprising a sense strand and an antisense strand. Each strand of the double-stranded nucleic acid molecule is 18 to 27 nucleotides in length. The antisense strand has complementarity to human ICAM nucleotide sequence comprising SEQ ID NO:439 and the sense strand has complementarity to the antisense strand. The double-stranded nucleic acid molecule further comprises at least two different modified nucleotides.

Applicants submit that the Office Action has not established a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, when combined must teach or suggest all the claim limitations. *See* MPEP §2143.

Here, there is no suggestion or motivation to combine the cited references. There is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. There must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the field of the invention would make the substitutions

required. That knowledge cannot come from the applicants' disclosure of the invention itself. *Diversitech Corp. v. Century Steps, Inc.*, 7 U.S.P.Q.2d 1315,1318 (Fed. Cir. 1988); *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987); *Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985).

An examiner can satisfy burden of the obviousness in light of combination "only by showing some objective teaching [leading to the combination]." *See, In re Fritch*, 972 F.2d 1260, 1265, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). Evidence of the teaching or suggestion is "essential" to avoid hindsight. *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir.1988). Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985). "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2d 1635, 1637 (Fed. Cir. 1998). The need for specificity is important. *See, e.g., In re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1317(Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed").

Elbashir and Tuschl teach siRNA technology generally, but fail to teach, mention, or suggest double-stranded nucleic acid molecules targeting a human ICAM nucleotide sequence comprising SEQ ID NO:439. Furthermore, Elbashir and Tuschl fail to teach any double-stranded nucleic acid molecules having two different modified nucleotides.

Nyce teach an antisense compound targeted to a ICAM gene but fail to teach, mention, or suggest double-stranded nucleic acid molecules targeting a human ICAM nucleotide sequence comprising SEQ ID NO:439.

Matulic-Adamic fails to cure the deficiencies of the cited references. Matulic-Adamic teaches generally modifications of ribozymes. Thus, not only does Matulic-Adamic fail to teach, mention, or suggest the use of double-stranded nucleic acid molecules, it fails to teach or suggest targeting human ICAM nucleotide sequence comprising SEQ ID NO:439.

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Nyce and Matulic-Adamic relate to antisense technology and ribozyme technology, respectively, which is not art the ordinary artisan would consider in making the claimed invention; it is non-analogous art. In order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." *In re Oetiker*, 977 F.2d 1443, 1446, 24 U.S.P.Q.2d 1443, 1445 (Fed. Cir. 1992).

Matulic-Adamic and Nyce are simply not pertinent to the problem addressed by the presently claimed compounds, which is to provide double-stranded nucleic acid molecules targeting human ICAM. Ribozyme technology and antisense technology modify RNA by mechanisms completely different and unrelated to RNAi. Despite the voluminous literature in the RNAi field, the applicants are unaware of a single instance in which a teaching regarding ribozymes or antisense has provided any insight into RNAi or been used in the study and development of double-stranded nucleic molecules that induce cleavage of target RNA by RNAi. Matulic-Adamic and Nyce are simply not references that one of ordinary skill in the art would consider in the development of the presently claimed molecules.

There is no suggestion to combine the references as the Office Action has done to target ICAM using double-stranded nucleic acid molecules as presently claimed. While a suggestion need not be express in the prior art, it must be clear and particular; broad conclusory statements about the teachings of multiple references is insufficient. *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 56 U.S.P.Q.2d 1456, 1459 (Fed. Cir. 2000). The mere identification of a target (Nyce) and a general mechanism for suppressing expression (Elbashir and Tuschl) without more is not the type of particularized suggestion necessary to sustain an obviousness rejection. The art must suggest the combination; it cannot come from the applicant's disclosure.[1]

Moreover, the cited references, alone or in combination, do not provide a reasonable expectation of success. The existence or lack of a reasonable expectation of success is assessed

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[1] Indeed, the Board of Appeals made this very point in a non-precedential opinion (copy enclosed), holding that one publication's teaching of

a) general rules for the design of new RNA enzymes capable of highly specific RNA cleavage,
b) successful tests of these RNA against target sequences, and
c) the conclusion that provided that transcribed sequences of a gene are known it should be possible to target one or more ribozymes against specific RNA transcripts,

and a second publication's teaching of the TGF-β sequence did not establish a *prima facie* case of obviousness of a claim to an anti-TGF-β ribozyme absent a suggestion or motivation found in the prior art to combine the references. The Board warned that the knowledge cannot come from the applicant's disclosure.

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from the perspective of a person of ordinary skill in the art at the time the invention was made. *See, Micro Chem. Inc. v. Great Plains Chem. Co.*, 103 F.3d 1538, 1547, 41 U.S.P.Q.2d 1236, 1245 (Fed. Cir. 1997). The inventors' ultimate success is irrelevant to whether one of ordinary skill in the art, at the time the invention was made, would have reasonably expected success. *See, Standard Oil Co. v. American Cyanamid Co*, 774 F.2d 448, 454, 227 U.S.P.Q. 293, 297 (Fed. Cir. 1985). It is impermissible to use hindsight. That is, using the inventors' success as evidence that the success would have been expected. *See, In re Kotzab*, 217 F.3d 1365, 1369, 55 U.S.P.Q.2d 1313, 1316,(Fed. Cir. 2000).

The priority date of the application is at least March 11, 2002. Therefore, as of March 11, 2002, it must be determined if one of ordinary skill in the art had a reasonable expectation of success in making a chemically modified double-stranded nucleic acid molecule comprising a sense strand and an antisense strand, wherein each strand of the double-stranded nucleic acid molecule is 18 to 27 nucleotides in length; wherein the antisense strand of the double-stranded nucleic acid molecule comprises a nucleotide sequence that is complementary to a human ICAM nucleic acid sequence comprising SEQ ID NO:439 and the sense strand is complementary to the antisense strand; and wherein the double-stranded nucleic acid molecule comprises at least two different chemically modified nucleotides.

In 2002 one of ordinary skill in the art knew:

1. That siRNA technology existed, *see,* Elbashir and Tuschl;
2. That antisense can be targeted to a ICAM transcript, *see,* Nyce;
3. That chemical modifications could be made to ribozymes, *see,* Matulic-Adamic.

One of ordinary skill in the art, as of March 11, 2002, would not have had a reasonable expectation of success of making a double-stranded nucleic acid molecule comprising a sense strand and an antisense strand about 18 to about 27 nucleotides in length, wherein the antisense strand comprises sequence complementary to human ICAM nucleotide sequence comprising SEQ ID NO:439, and wherein the double-stranded nucleic acid molecule further comprises at least two different chemically modified nucleotides. The cited references merely demonstrate that double-stranded nucleic acid technology existed, that ICAM could be targeted with antisense, and that chemical modifications could be made to ribozymes which are distinct from the double-stranded nucleic acid molecules of the invention. At the time of the invention, the successful use of chemically modified short double-stranded nucleic acid molecules in

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mammalian systems was highly speculative at best. Importantly, the art did not recognize that modification with at least two different chemically modified nucleotides could be tolerated in double-stranded nucleic acid molecules. Application of this technology to targeting human ICAM nucleotide sequence comprising SEQ ID NO:439 would not be envisioned by one of skill in the art with any reasonable expectation of success. Therefore, in the absence of any teaching whatsoever of a double-stranded nucleic acid molecule as presently claimed, one skilled in the art would have no reasonable expectation of success of making such molecule.

For the reasons set forth above, Elbashir, in view of Nyce, Tuschl, and Matulic-Adamic do not teach or suggest making a double-stranded nucleic acid molecule comprising a sense strand and an antisense strand about 18 to about 27 nucleotides in length, wherein the antisense strand comprises sequence complementary to human ICAM nucleotide sequence comprising SEQ ID NO:439, and wherein the double-stranded nucleic acid molecule further comprises at least two different chemically modified nucleotides with a reasonable expectation of success. Therefore, the cited references do not render the present invention obvious. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejection.

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, she is encouraged to contact the undersigned as indicated below.

Respectfully submitted,

Date: December 6, 2005

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